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Prions, prionoids and pathogenic proteins in Alzheimer disease

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Like patients with prion disease, Alzheimer patients suffer from a fatal, progressive form of dementia. There is growing evidence that amyloid- β (A β) aggregates may be transmissible similar to prions, at least under extreme experimental conditions. However, unlike mice infected with prion protein (PrP) prions, those inoculated with A β do not die. The transmission of A β and PrP thus differs conspicuously in the neurological effects they induce in their hosts, the difference being no less than a matter of life and death. Far from being a mere academic nuance, this distinction between A β and PrP begs the crucial questions of what, exactly, controls prion toxicity and how prion toxicity relates to prion infectivity.

Prions in Neurological Disease

Stanley Prusiner introduced prions in 1982 as the self-replicating forms of the prion protein that accumulate in certain transmissible diseases of the central nervous system, such as scrapie and Creutzfeldt-Jakob disease.¹ Although prions represent novel infectious agents lacking pathogen-encoded nucleic acids, their discovery relied upon a century-old paradigm, formalized into postulates by Robert Koch, for identifying pathological microbial agents. A key concept in Koch's postulates is that the microbe responsible for a given disease must cause that same disease when inoculated into a susceptible host. In prion disease, the afflicted individual suffers from a progressive deterioration in neurological function that culminates, inevitably, in death. By systematically sifting through brain extracts from scrapie-infected hamsters, Prusiner found that the deadliest inoculates contained fibrillar aggregates of a proteolytic fragment of the prion protein, PrP²⁷⁻³⁰. We now know that this fragment is derived from the scrapie isoform of the prion protein, PrP^{Sc}, an aggregated, alternatively folded conformer of the cellular prion protein, PrP^C.²

In 2000 Lary Walker first demonstrated that intra-cerebral inoculations of brain extracts from amyloid plaque-containing brain tissue from Alzheimer patients accelerate amyloid plaque deposition and β -amyloidosis in transgenic mice expressing human A β proteins.³ The acceleration of β -amyloidosis by inoculates containing A β fibrils, which form amyloid plaques, has

been replicated in at least four other laboratories using inoculates from humans, several lines of plaque-forming transgenic mice and, most recently, fibrillar synthetic A β aggregates and synthetic A β dimers.⁴⁻⁷

While these results indicate that fibrillar conformers of A β proteins can self-replicate in susceptible hosts, it is still unclear whether such replication can be maintained over multiple serial passages from one animal to another. The latter is an integral part of the definition of a "prion." For the sake of the following discussion, we will refer to PrP^{Sc} as the aggregated form of PrP^C found in transmissible spongiform encephalopathies (TSEs), and to "prions" as the infectious agent of TSEs as measured with microbiological methods. In this frame of reference, prions are composed of PrP^{Sc}, but not all PrP^{Sc} is necessarily infectious.⁸

Infectious Agents, Prions and Prionoids

In 1966 Carlton Gajdusek astonished the scientific world with the claim that the fatal degenerative disease kuru was transmitted through ritualistic cannibalism among the Fore peoples of New Guinea;⁹ the proposal that the elusive infectious agent in kuru was a prion was no less surprising. Now, however, the radical properties ascribed to prions threaten to undermine the original meaning of "infectious agent." In the following discussion, an infectious agent transmits a disease causing deficits in the host that are the same as those in the donor and share the same pathophysiology. Simply put, infectious agents are the biological basis of ill health that can be passed between living beings.

Prions fulfill the above definition since they were initially discovered as true infectious agents using microbiological methods. However, many other proteins can aggregate into geometrically arranged structures that can seed—in vitro and in vivo—compartments containing the parent protein in a monomeric soluble state.

Simply equating the capability of seeding with the term "prion" is an oversimplification. Any inorganic crystal can seed a supersaturated solution of its cognate salt, whereas bona fide prions have caused epidemics in sheep, cows, mink, felines and humans (kuru, as well as iatrogenic and "variant" Creutzfeldt-Jakob disease). Because of their flagrant infectious traits—communicability and contagiousness—the agents of these diseases were not recognized as prions for many decades, and many pre-eminent scientists deemed them to be "slow viruses."

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Since none of the newly discovered seeded aggregates have yet been shown to be infectious (i.e., communicable or contagious) under natural conditions, we deem it prudent to refer to them as “prionoids.”^{10,11} Maintaining a distinction between prions and prionoids implies the existence of underlying biological processes that govern the natural transmission of diseases between organisms, including the sophisticated mechanisms by which extraneural inoculations of prions subvert the immune system to reach and damage the brain (reviewed by Aguzzi and Calella¹²).

Fortunately, there is no indication that such processes exist for A β prionoids. However, the demonstration of inter-individual transmissibility would warrant upgrading the status of such agents to bona fide prions, as seems very likely to occur in the case of AA amyloid.¹³

Prionoids and Pathogenic Proteins in Neurodegenerative Diseases

Prior to the era of molecular genetics, neurodegenerative diseases of the elderly were defined by the types of misfolded proteins that accumulate as insoluble deposits in the brain. The deposits consisted of highly ordered stacks of β -sheets, which is the physical definition of amyloid. Each type of amyloid resides in a characteristic nuclear, cytoplasmic or extracellular compartment. With the advent of molecular genetics came the discovery of causal genes linked to many of these neurodegenerative diseases and, in a remarkably large number of instances, a given gene encoded the very protein comprising the amyloid fibrils that characterized the neuropathology in the disease.

These diseases became known as protein misfolding disorders, because the causal genes encoded the misfolded proteins comprising the amyloid lesions. In every instance, the misfolded proteins acquire secondary structure— β -sheets—that is absent under normal conditions. Protein misfolding in neurodegenerative diseases refers to conditions in which parent proteins take on novel β -sheet secondary structure. The acquisition of novel secondary structure distinguishes protein misfolding disorders from other diseases caused by mutations that alter protein conformation, such as sickle cell anemia.

With the exception of PrP^{Sc}, there is no experimental evidence that the prions or prionoids in neurodegenerative diseases are the pathogenic proteins [star (*) proteins] inducing the neurological deterioration that devastates patients. For a hundred years, neurofibrillary tangles—the intracellular amyloid inclusions that form when tau takes on novel β -sheet structure—were believed to induce neuron death and impair cognition. However, in 2005 this hundred year-old hypothesis was disproven when it was shown that reducing soluble tau in a neurodegenerative mouse model with neurofibrillary tangles led to the cessation of neuron loss and the improvement of memory function, in spite of the startling observation that the neurofibrillary tangles kept accumulating, reminiscent of prionoids.¹⁴ The negative case for β -amyloid plaques containing *proteins stems from multiple lines of evidence, including the failure of Alzheimer patients to improve following A β immunotherapy that nonetheless successfully removed amyloid plaques,¹⁵ and the ability of immunotherapy to reverse deficits in

mice without changing plaque load.^{16,17} Compared with the proteins comprising amyloid lesions, prions, and prionoids, relatively little is known about *proteins and their mechanisms of action.

By far the best understood among these disorders is familial ataxia type 1. Ataxin-1 causes familial ataxia type 1 when extraneous trinucleotide repeat sequences expand the existing polyglutamine tract to form PolyQ/ataxin-1.¹⁸ Patients and mice expressing PolyQ/ataxin-1 develop nuclear inclusions and progressive ataxia. PolyQ aggregates are prionoids, since the application of PolyQ aggregates to cultured neurons nucleates the formation of intracellular PolyQ amyloid.¹⁹ In mice carrying a knocked-in expanded PolyQ tract, the severity of the neurological abnormalities and neurodegeneration corresponds inversely with the number of inclusions,²⁰ and the abolition of the inclusions through the mutation of a ubiquitin ligase, which promotes the aggregation of misfolded proteins, accelerates the disease.²¹ These studies indicate that the elimination of the inclusions will not prevent ataxia in familial ataxia type 1.

The conclusion that the removal of the inclusions would not cure familial ataxia type 1 prompted Harry Orr and Huda Zoghbi to search for the pathogenic form of PolyQ/ataxin-1 causing the neurological abnormalities in the disorder. Discovering the mechanism by which PolyQ/ataxin-1 damages neurons emerged from understanding the normal physiological roles of ataxin-1, which is a nuclear protein. The pathogenic form of PolyQ/ataxin-1 is not a misfolded form of ataxin-1; it contains no novel secondary structures, no β -sheets that are not normally present in the brain. Its pathological effects arise from alterations in its binding affinities with its normal nuclear partners, the transcriptional regulator Capicua and the regulator of RNA splicing RMB17,²² leading to changes in the transcriptome that, presumably, affect neuronal function and viability. Thus, the pathogenic form of PolyQ/ataxin-1 is not a prionoid; it is neither a misfolded protein nor a soluble aggregate of the parent protein. This may prove to be a profoundly important lesson for the entire field of neurodegenerative disease research.

A Puzzle and Two Hypotheses

Both patients with prion disease and Alzheimer disease suffer from fatal, progressive forms of dementia. However, while mice infected with PrP prions die, those inoculated with A β prions do not. Only two hypotheses can explain the stark contrast between the fatality rates caused by PrP and A β inoculations in mice.

- **Hypothesis 1: All aggregated proteins (prions and prionoids) are bad.** Aggregates are pathogenic, but different aggregates exert their effects on different cellular pathways. For example, the pathogenic pathway for A β aggregates in humans, distinct from that of PrP prions, may not exist in mice.

- **Hypothesis 2: Not all aggregates are bad.** Aggregates are not invariably pathogenic; rather, variants of parent proteins (*proteins) cause the cellular dysfunction that leads to a neurological illness (Fig. 1). These pathogenic variants need not be misfolded or aggregated forms of the parent proteins.

Recent advances in our understanding of the neurotoxicity of PrP and A β favor Hypothesis 2, as discussed below.

Neurotoxicity of PrP

In prion disease catastrophic brain dysfunction is associated with a global decrease in protein production, resulting from the dysregulation of eIF2 α , a mammalian translation initiation factor.²³ This fascinating discovery is presumably the mechanism by which PrP prions ultimately induce neurotoxicity.

However, eIF2 α is localized within the cytosol whereas infectious prions are extracellular. Therefore, we are still left wondering how prions containing pathologically aggregated PrP^{Sc} can possibly exert actions that originate from the extracellular milieu, derange protein folding in the endoplasmic reticulum, induce a surprisingly vigorous unfolded protein response, and eventually quench cytosolic translation of proteins. It is hard not to conclude that eIF2 α repression likely represents a downstream effector of a pathogenic cascade that is initiated by molecularly and topologically distant events.

There has been recurrent discussion as to whether the self-replicating material in prion disease (the “prion”) is physically identical with the neurotoxic entity. In this context, John Collinge has recently proposed the term “PrP^L” to denote a hypothetical moiety that may be neurotoxic yet differs from PrP^{Sc}.²⁴

However, the idea that PrP may produce neurological disease without the generation of infectivity dates back to 1990 when transgenic mice that spontaneously developed prion disease were created. These mice expressed PrP carrying a mutation linked to a familial prion disease, developed ataxia, lethargy and rigidity, and invariably died, but their brains contained few or no infectious prions, suggesting that “an inborn error of PrP metabolism could produce neurologic disease without the generation of infectivity.”²⁵ It is possible, and indeed very likely in our view, that PrP^{Sc} and the various non-infectious neurotoxic variants of PrP, which include PrP with supernumerary octapeptide repeats²⁶ and PrP versions with interstitial deletions of the “hinge” region between the unstructured N-terminus and the globular domain,²⁷ activate neurotoxic pathways converging with those triggered by prion infection (Fig. 2).

Neurotoxicity of A β

Our understanding of the neurotoxicity of A β lags behind that of PrP, because animal models that recapitulate all the facets of Alzheimer disease, which are needed to assay the human relevance of pathological A β , do not exist. In humans, the pathological transformation of A β initiates a process that involves the accumulation of amyloid plaques and often leads to a fatal neurodegenerative condition. In mice, the formation of pathological A β may induce amyloid plaque deposition, which reflects the

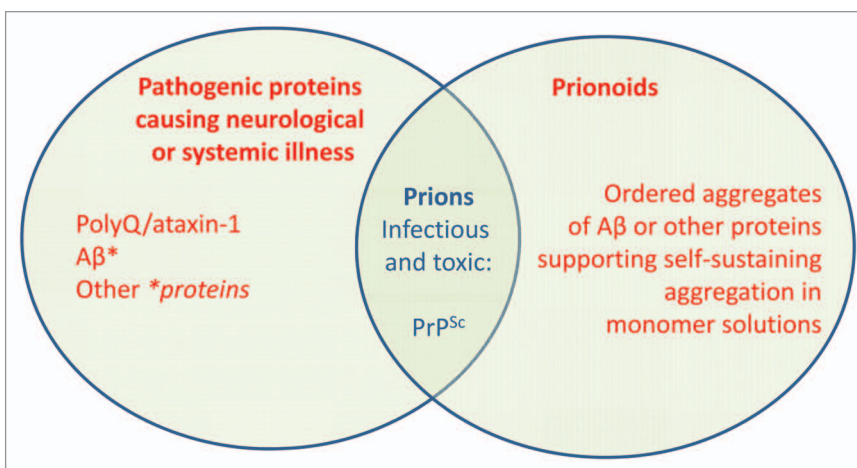


Figure 1. Prions, prionoids and pathogenic proteins in neurodegenerative diseases. PrP^{Sc} is considered to be the transmissible agent of the prion causing scrapie, Creutzfeldt-Jakob disease and related spongiform encephalopathies. Nucleating fibrillar protein aggregates (“prionoids”) are found in many neurodegenerative diseases. With the exception of PrP^{Sc}, there is little evidence in mice or humans linking prionoids in the brain to the pathophysiological processes that cause the disorders connected with these proteins. Instead, accumulating data indicate that the brain dysfunction and neurological signs associated with these illnesses are caused by non-fibrillar variants of the parent proteins (*proteins). In the case of A β , brain dysfunction in mice and CSF tau abnormalities in humans are strongly associated with a soluble 56-kDa assembly, A β *. The existence of other A β * molecules has not been excluded. The *proteins need not be misfolded in the sense of adopting novel secondary structure, which invariably involves β -sheets. PolyQ/ataxin-1 is the best example. Distinguishing between prionoids and *proteins, and understanding how *proteins cause neurological illness, will advance our progress in treating these profoundly devastating and fatal disorders.

presence of A β prionoids. It is astonishing that the accumulation of A β prionoids in the vast majority of mice does not lead to overt neurodegeneration, except in the immediate vicinity of amyloid plaques.^{28–30} In mice lacking nitric oxide synthase 2, the accumulation of A β prionoids is associated with neuron death in the CA3 but not the CA1 hippocampal subfield,³¹ but in humans CA3 is spared while CA1 is not,³² calling into question the relevance of this form of neuron death. Whether neuron death in this model is due to A β prionoids is also unknown. Fatality, when present, is strain-dependent, and can occur in the absence of amyloid formation, suggesting the existence of a neurotoxic species, which may not necessarily be congruent with the self-propagating species.³³ The biochemical identity and cellular effects of this form of A β remain unknown.

Two types of cognitive dysfunction develop in mice over producing A β . One type is found in mice with aggressive amyloid deposition—an excessive amount of A β prionoids—in which the amassed amyloid plaques and their surrounding cytopathology act like a gigantic space-occupying lesion in the brain.²⁸ No neurons remain within plaque cores, and tortuous, dystrophic neurites and dendrites partially denuded of spines reside in the 50-micron halo surrounding the cores (reviewed by Ashe and Zahs³⁴). It is therefore not surprising that, beyond a certain threshold, cognition varies inversely with plaque load. However, the density of amyloid plaques required to produce this effect is rarely reached in Alzheimer disease, which may explain why the

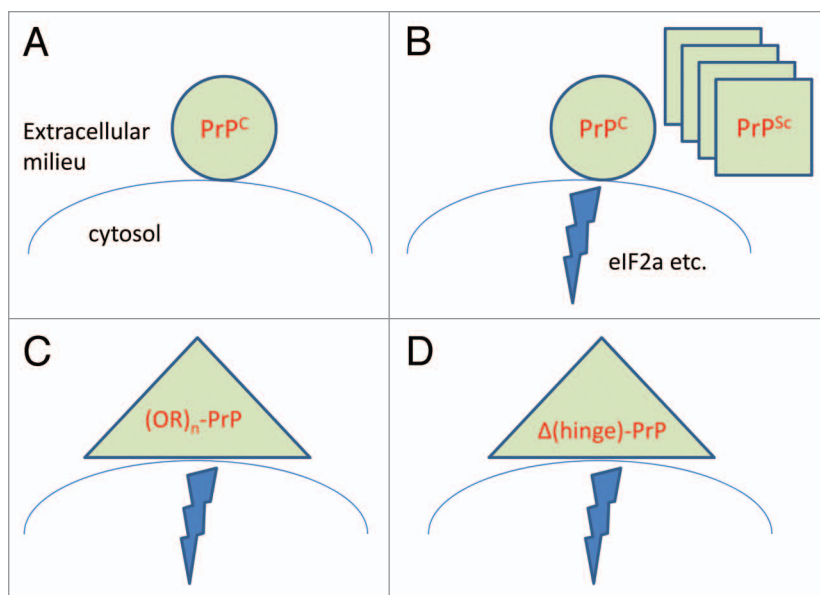


Figure 2. The cellular prion protein is absolutely required for the toxicity of infectious prions (A),³⁹ implying that PrP^{Sc} exerts neurotoxicity by docking to PrP^C (B). This toxicity may also be elicited by PrP variants occurring naturally, such as PrP carrying supernumerary octapeptide repeats (C), or experimentally constructed toxic variants such as PrP versions carrying deletions of the hinge region (D). It was recently discovered that prion infection results in a chain of events that ultimately quenches protein translation,²³ but it remains to be seen whether the toxicity elicited by PrP mutants (C and D) utilizes the same pathway.

links between plaques and neuron loss or cognition are tenuous at best.^{35,36} An excessive accumulation of Aβ prionoids in mice can result in cognitive deficits that are related to the space-occupying effects of the amyloid plaques, but this is distinct from the mechanism by which most of the neuronal dysfunction and neurodegeneration occurs in humans with β-amyloidosis or Alzheimer disease.

The other type of cognitive dysfunction occurs independently of plaques or neuron loss, and appears to be due to a non-fibrillar 56-kilodalton Aβ assembly termed Aβ*56.³⁷ Aβ*56 is a putative dodecamer most likely formed by the clustering of four Aβ trimers. Isolates of fibrillar Aβ in the brain do not contain Aβ*56 (Liu P and Ashe K, unpublished data). It is unlikely that Aβ*56 acquires novel β-sheet structure, because the compositional unit, Aβ trimers, is present even in young mice.³⁷ The absence of novel β-sheet structure in Aβ*56 argues against it being a prionoid, although formal demonstration will require transmission experiments. Aβ*56 induces no overt neurodegeneration, and yet alters cognition by disrupting long-lasting synaptic plasticity by an as yet unknown mechanism.³⁸ In humans, Aβ*56 can be measured in the CSF, where it increases with normal aging and correlates moderately strongly with the microtubule-binding protein tau (M. Handoko, M. Grant, A. Wallin, K. Blennow and K. Ashe,

unpublished data). Tau is released into the CSF, through a process that remains unclear, when neurons malfunction. CSF tau correlates weakly or not at all with CSF Aβ1–42, which reflects β-amyloidosis and Aβ prionoids.

Although it was tempting to postulate that Aβ*56 triggers a sequence of events that leads to the conversion from asymptomatic aging to mild cognitive impairment or Alzheimer disease, which coincides with the onset of overt neurodegeneration and neuron loss, this prediction was not borne out in a large longitudinal study (Handoko M, Grant M, Petersen R and Ashe K, unpublished data). Thus, Aβ*56 disrupts neuronal function in mice and is linked to neuronal malfunction in humans, but is insufficient to induce overt neurodegeneration in either species.

In the absence of animal models, harboring Alzheimer-related mutations exclusively, that exhibit the full spectrum of disease, beginning with subtle neuronal dysfunction and culminating with fatal cognitive devastation, the question of whether asymptomatic β-amyloidosis requires Aβ*56 to develop into full-blown Alzheimer disease cannot be addressed experimentally. It is possible that one or more non-prionoid form of Aβ triggers neuronal dysfunction and neurodegeneration in Alzheimer disease. Discovering these pathogenic forms will depend upon the creation of high fidelity model systems of Alzheimer disease.

Conclusion

In bona fide prion diseases, a very large body of evidence links the aggregated form of PrP, PrP^{Sc}, to both prion infectivity and prion neurotoxicity. However, non-infectious, yet neurotoxic, variants of PrP occur naturally and more such variants have been constructed experimentally, indicating that the phenotypic expression typical of prion diseases can be triggered by events occurring downstream of prion infection. There is little evidence in mice or humans linking the neurological effects of Aβ to the nucleating forms of this protein, while emerging data point to a specific non-nucleating form of Aβ, Aβ*56, that produces some of the neurological signs of disease. However, Aβ*56 is not sufficient to induce the inexorable neurological deterioration that characterizes Alzheimer disease, indicating that other critical factors or forms of Aβ work in collaboration with Aβ*56 to destroy the brain. Curing prion and Alzheimer disease will depend upon developing a deeper understanding of the pathogenic forms of PrP and Aβ that cause the brain dysfunction underlying these deadly illnesses.

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